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Influence of Cancer and Its Severity on Vagal Nerve Activity Assessed By Time Domain Measures of Heart Rate Variability.

Shilpa N Bijoor[1], Subbalakshmi N K[1]*, and Sourjya Banerjee[2].

[1]Department of Physiology, [2] Department of Radiotherapy and Oncology, Kasturba Medical College and Hospital, Mangalore, Manipal University, Karnataka, India.

ABSTRACT

Recent research is probing in to association between poor prognosis of cancer and vagal nerve activity. To investigate the influence of severity of cancer on Indices of vagal function namely E:I ratio and r-MSSD. 184 patients with solid malignant tumor and 150 controls were studied**.** Severity of cancer was defined based on the TNM staging**.** Accordingly study subjects were divided into: Early stage **(**TNM Stage I and II combined) and Advanced stage (TNM stage III and IV combined). E: I ratio during deep breathing and r-MSSD during resting were determined from one minute lead II electrocardiogram. Data was analyzed using Students unpaired t, Mann- Whitney U statistic and Kruskal Wallis tests. p value <0.05 considered significant. **Results:** E:I ratio, r-MSSD was lower in cancer patients compared to control ($p<0.0001$). E:I ratio and r-MSSD was lower in cancer patients with early and advanced stage of cancer compared to control ($p<0.0001$). In study subjects E:I ratio and r-MSSD was lower in advanced stage compared to early stage ($p<0.05$; 0.0001, respectively). Vagal function is reduced in cancer patients compared to healthy subjects. Severity of cancer affects vagal activity.
Keywords: Vagal nerve activity, Cancer severity, TNM stages

Corresponding author

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INTRODUCTION

Heart rate variability (HRV) is a degree of fluctuation in the length of intervals between the heart rate. Indices of HRV are used extensively as a measure of autonomic function of the heart [1]. Heart rate varies with respiration in a healthy individual. It increases with inspiration and decreases with expiration the so called respiratory sinus arrhythmia. HRV with deep breathing is a sensitive measure of parasympathetic activity [2]. Parasympathetic activity is affected at the earliest in autonomic dysfunction patients than sympathetic activity [3]. Thus measuring vagal function gives a better indication of autonomic dysfunction at the earliest. It is well known phenomenon that HRV with deep breathing is liable clinical test for early detection of diabetic autonomic neuropathy [4]. Reduced HRV in cardiology is one of the predictors of death in post myocardial infarction patients [5]. Clinical utility of measurement of HRV is also explored in neurology, psychiatry and is now extending in to cancer [6]. Recent research in cancer is probing in to association between cancer and vagal function.

Cancer incidence rates and cancer related deaths have been increasing despite of several medical developments. Identifying new prognostic factors is important for guiding treatments and preventing metastasis of cancer. The experimental studies in animals have observed that cancer induces cardio-myocyte remodeling and hypo-innervations of the heart [7]. In vagotomised animals enhanced metastasis and worse prognosis of cancer was observed [8-9]. Vagal nerve innervates most of the organs where cancer is developed. In our previously conducted pilot study on status of vagal function in cancer patients, we had observed that E: I ratio a known index of vagal function was lower in patients with solid malignant tumor compared to control [10]. To further elucidate the association between vagal nerve activity and cancer pathology this study was undertaken to find the influence of severity of cancer on two indices of vagal function namely, E:I ratio and r-MSSD.

MATERIALS AND METHODS

This was a hospital based cross sectional study. This study was carried out in the Department of Oncology at Kasturba Medical College and Hospital, Attavar, Mangalore after approval by the Institutional Ethical Committee and informed consent from study participants.

Study Subjects

A total of 187 cancer patients were recruited to the study: 100 men and 87 women. The median age was 54 years (range 40-68 years). Three types of solid malignant tumors were pooled together for the study: Head & Neck cancer (n=87), Gastrointestinal cancer (n=42) and Gynecological cancer (n=58). The study subjects were divided in to two broader subgroups: Early stage of cancer group (stage I and II combined) and Advanced stage of cancer group (stage III and stage IV combined).

Control group

Consisted of 150 healthy individuals matched for age and gender of study subjects.

Inclusion criteria for study subjects

Cancer patients basically with solid malignant tumor who were not yet put on any treatment.

Exclusion criteria

Patients with history of cardiovascular disease, diabetes and in patients in whom tumor extended up to cervical sympathetic chain or any factor known to affect heart rate variability were excluded.

Study protocol

The entire procedure was explained to the study participants prior to commencement of the tests. The tests for vagal functions were performed in the morning in supine position after subjects were completely relaxed. All the subjects in the study and control groups were subjected to clinical examination. In the study

subjects based on histo-pathological reports and as diagnosed by the oncologist, AJCC staging of each cancer patient was documented.

EXPERIMENTAL

Staging of cancer patients

In the present study four different stages of cancer was defined as per the TNM system proposed by the American Joint Committee on cancer, the most frequently used system. In this system, T reflects primary tumor size and extension; N is based on the size, number, and location of cervical lymph node metastases; and M represents more distant metastases [11] .

Assessment of baseline characteristics

The weight and height of all the subjects recruited in to the study were measured. Body mass index was calculated using the formula: weight in kilograms (kg) divided by height in meters (m) squared [(12)]. Blood pressure was measured using sphygmomanometer in sitting position and mean of the two readings were taken as blood pressure. And heart rate of each subject was obtained from one minute resting lead II electrocardiogram in supine position by counting total number of R-R intervals.

ASSESSMENT OF VAGAL NERVE FUNCTION

Assessment of Expiratory: Inspiratory ratio (E: I ratio) in response to deep breathing

Before beginning the test, all the subjects were trained to breathe at a rate of six respiratory cycles per minute. The examiner raised his hand to signal the start of each inhalation and exhalation, then lead II ECG was recorded with speed of 25mm/sec for one minute (60secs), while the subject breathed as instructed (Cardiart 108T/MKVII, BPL Ltd. Bangalore, Karnataka, India). All R-R intervals were measured precisely. The longest R-R interval during expiration and the shortest R-R interval during inspiration was expressed as Expiratory: Inspiratory ratio [13-14].

Assessment of r-MSSD

r-MSSD was estimated from one minute resting lead II ECG. All of the R–R intervals were measured from one minute resting electrocardiogram was computed. r-MSSD was estimated with suitable statistical functions using Microsoft Windows XP Professional (Microsoft Corporation, Redmond, WA, USA)[15] .

Statistical Analysis

Data was analyzed with appropriate statistical tests. Students unpaired t test was applied to compare indices of parasympathetic function between study and control group. Kruskal Wallis test followed by Tukey-Kramer multiple comparison test was applied to assess E:I ratio and r-MSSD between early and advanced stage of cancer compared to control group. The level of significance was obtained by two tailed test. p value < 0.05 was considered as significant.

RESULTS

Data is represented as mean ± SD. Data on baseline characteristics and vagal nerve function between study and control group is presented in Table 1. Data on vagal nerve function among early and advanced stage of cancer compared to control group is presented in Table 2.

Comparison of baseline characteristics and vagal nerve functions between study and control group

Body mass index was lower in study group compared to control ($p<0.0006$, Table 1). E:I ratio and r-MSSD was significantly lower in study group compared to control group ($p < 0.0001$, Table 1). Age, blood pressure and heart rate of study subjects did not differ significantly compared to control group (Table 1).

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Table 1. Comparison of baseline characteristics and vagal nerve functions between study and control group (values are represented as mean ± SD)

Variables	Control group (n= 150)	Study group (n= 187)	t /uvalue	p value
Age (years)	51.57±8.56	53.00±10.11	12638	0.1015
Body mass index (kg/m^2)	21.55±2.91	19.68±3.35	3.772	0.0006
Systolic blood pressure (mmHg)	119.61±7.69	119.06±13.08	13428	0.6850
Diastolic blood pressure (mmHg)	76.93±5.24	77.40±6.70	13353	0.5499
Resting heart rate (beats/min)	72.32±5.07	73.62±7.61	12122	0.0790
E:I ratio	1.35±0.9	1.15±0.10	1.784	0.0001
r-MSSD	40.23 ± 12.98	28.77 ± 7.48	5635.5	0.0001

Note: t = unpaired't' test, u= Mann- Whitney U statistic

Comparison of vagal nerve functions between early stage and advanced stage of cancer in study group compared to control group

Data on comparison between early stage and advanced stage of cancer in study group compared to controls is presented in Table 2. E:I ratio and r-MSSD was significantly lower in early stage and advanced stage of cancer compared to control ($p<0.0001$, Table 2). In study group, E:I ratio and r-MSSD was significantly lower in advanced stage of cancer compared to early stage ($p<0.05$; 0.0001, respectively, Table 2).

Table 2: Comparison of vagal nerve function among different stages of tumor and control group (values are represented as mean ± SD)

Parameters	Control (n=150)	Early stage (n=59)	Advanced stage (n=128)	KW	p value
E:I ratio	1.35±0.9	1.17±0.16***	1.14±0.07***†	209.27	0.0001
r-MSSD	40.23±12.28	33.09±9.86***	26.77±5.03***‡	109.65	0.0001

Note: KW= Kruskal Wallis Test. ***p< 0.001 compared to control, † p< 0.05 compared to early stage, ‡p< 0.001 compared to early stage

DISCUSSION

In the present study, E:I ratio and r-MSSD the known indicators of vagal function were significantly lower in study subjects compared to control. Vagal activity is known to decline with aging [16], lower to certain extent in female gender [17] and adversely affected by comorbid conditions such as diabetes mellitus and cardiovascular disease [18]. Similarly certain chemotherapy drugs are also known to affect cardiac autonomic function [19]. But in the present study, study group and controls were comparable with regard to age and gender. Indices of vagal function were quantified in clinically diagnosed patients with cancer but prior to any chemotherapy treatment. Cancer patients with known comorbid conditions which may affect vagal function were excluded. Therefore lower E:I ratio and r-MSSD observed in our study population compared to healthy subjects suggests that cancer pathogenesis and vagal function are interlinked. Decouck et al too had observed reduced vagal function in cancer patients mainly comprising of patients with lung, ovary, pancreas as primary site of tumor [20]. Our study populations were mainly with gynecological, gastrointestinal, head and neck cancer. However one common factor prevails in our study subjects and Decouck et al study population that is both were with solid malignant tumor even though primary site of tumor were different. All these viscera are richly supplied with autonomic nerve fibers. Therefore may get influenced by altered visceral environment owing to presence of malignant tumor.

To further investigate the association between severity of cancer and vagal function, we assessed the vagal function of study subjects in advanced stage of cancer and early stage of cancer compared to controls. It was observed that vagal function of early and advanced stage of cancer was lower compared to controls. And advanced stage cancer patients had lower vagal nerve activity than patients with early stage of cancer. According to AJCC staging I and II combined that is patients with early stage of cancer had lesser tumor burden. They were with relatively smaller tumor size and fewer lymph node metastasis. On the other hand advanced stage patients had relatively larger tumor size and were with greater lymph node metastasis. In addition they were with metastasis to distant organs. This finding suggests that vagal function deteriorates as

the tumor burden increases in terms of growth of tumor in size, greater involvement of lymph nodes and spreading of cancer cells in to distant organs. De Couck et al also observed similar result using r-MMSD an indicator of vagal function [21]. However their study population had included comorbid conditions such as diabetes and cardiovascular diseases which is known to affect vagal function unlike our study population who were solely with cancer. Therefore our study mainly highlights the association between cancer pathogenesis and vagal function. In oncology, cancer stage is the most important factor used in judging the prognosis of the patient. Thus the findings of our study suggest the possibility of considering assessment of vagal function as a new prognostic factor in relation to severity of cancer. However further experimental and prospective studies are required in this front to employ it in clinical set up.

Our study is with certain limitations. Considering the number of cancer patients increasing with time our sample size was relatively small. So data from three different sites were pooled. However, even in the relatively small sample size our study provides clear evidence for influence of solid malignant tumor on vagal activity.

CONCLUSION

Vagal function is reduced in cancer patients compared to controls. Severity of cancer affects vagal activity.

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